



CASE REPORT

Prenatal Diagnosis of Congenital Harlequin Ichthyosis with Two- and Three-Dimensional Ultrasound in the Third Trimester



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Harlequin ichthyosis (HI) is a rare congenital fetal skin keratinization disorder with an autosomal recessive inheritance. HI has specific sonographic features in the antenatal period. Several reports of prenatal sonographic diagnosis of HI have demonstrated its characteristic facial features that include a persistently open mouth and ectropion, with echogenic amniotic fluid and restriction of limb movements. Here, we report the case of a fetus in the 3rd trimester with these syndromic features identified by two- and three-dimensional sonography. Our ultrasonographic observation of membranes arising from the skin surface is particularly noteworthy. No prior case in which HI has been characterized by three-dimensional ultrasonography has been reported.

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Introduction

Harlequin ichthyosis (HI) is a rare and lethal fetal anomaly. At birth, a newborn infant with HI has thickened, yellow-colored, armor-like skin with fissures that divide the skin

into polygonal sections. Facial anomalies include ectropion (eversion of the eyelids), eclabium (eversion of the lips), and a large, round, and wide open mouth. The nose and ears are hypoplastic. The limbs are usually short and held in a fixed, flexed position [1].

The first case of prenatal diagnosis of HI was reported in 1983 [2]. As the patient had a family history of two previously affected infants, the diagnosis of HI was based on fetal skin biopsies under fetoscopy. However, the use of this traumatic method for the prenatal diagnosis of HI is limited to pregnant women with a previously affected

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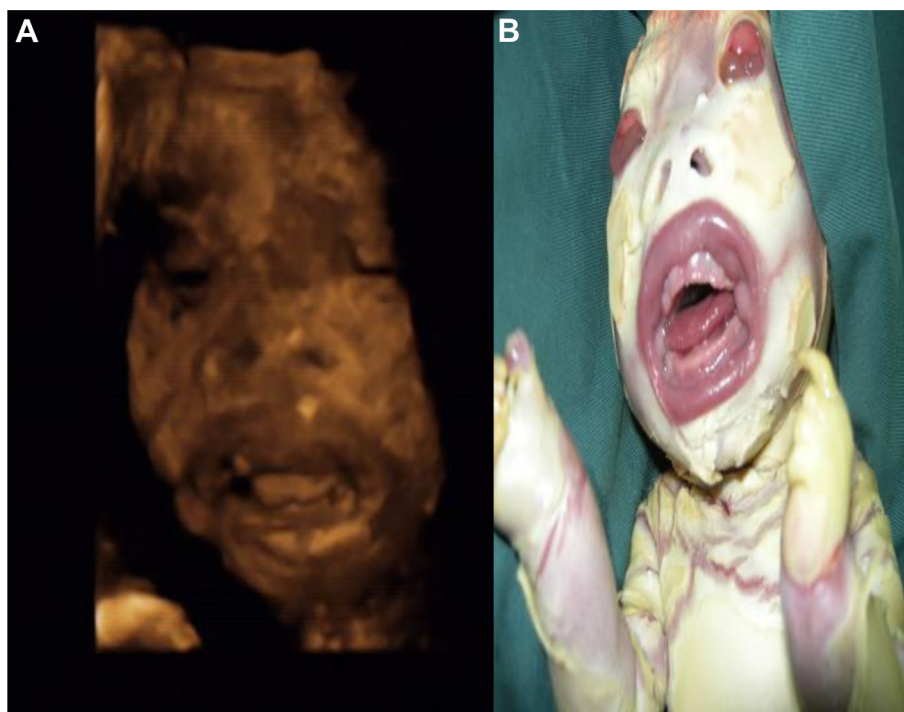


Fig. 1 Characteristic facial features of HI. (A) Three-dimensional image of the fetus with an open mouth, a protruding tongue, and open eyes and (B) photograph of the neonate upon delivery. HI = harlequin ichthyosis.

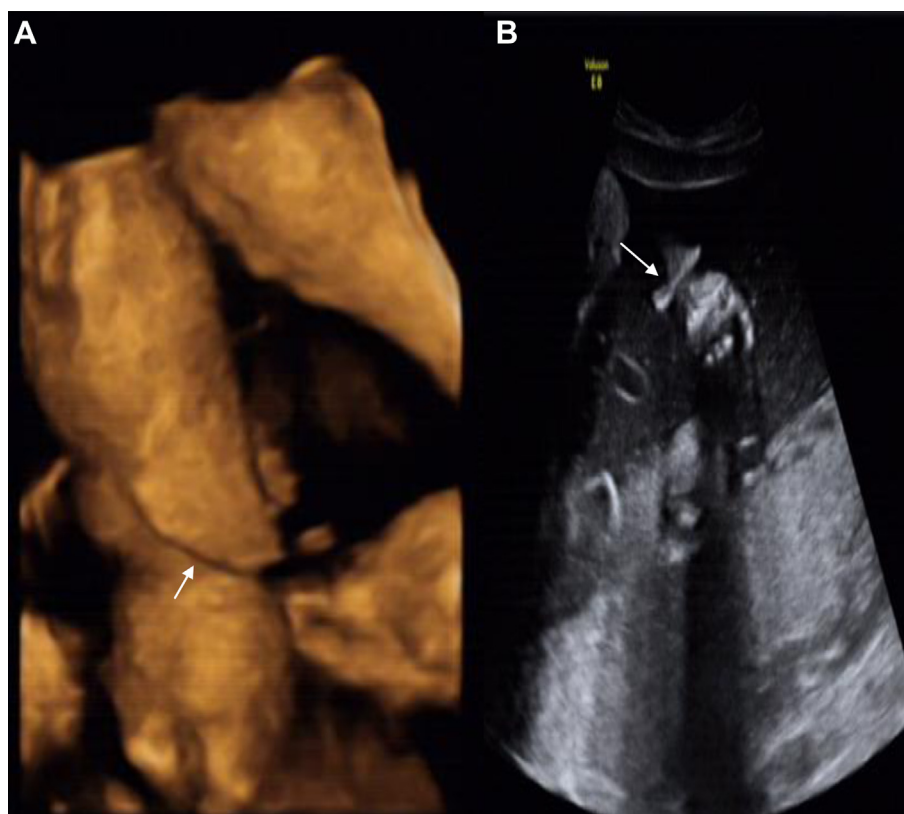


Fig. 2 Membrane arising from the skin surface of the fetus: (A) three- and (B) two-dimensional views. Membrane location is indicated by arrows.

Table 1 Review of the prenatal sonographic features of HI.

Case	Family history	Ga	Eyes	Mouth	Nose	Ears	Skin	Hands	Feet	Amniotic fluid volume	Intra-amniotic debris	Fetal growth
Present case	No	34 ⁺⁶	—	Open	Flat	—	Gloating and arising membrane	Fixed flexion	Short toes	Polyhyd.	+	IUGR
Kudla and Timmerman (2010) [15]		26	Ectropion	Open	Flat	—	—	Fixed flexion	Short digits	Polyhyd.	—	IUGR
Holden et al (2007) [12]	+	32	Normal	Normal	Normal	Poorly formed	Extremities edema	Fixed flexion	Fixed shortened	Normal	+	—
Zapałowicz et al (2006) [14]	No	25	Ectropion	—	Flat	—	—	—	—	—	—	Normal
Vohra et al (2003) [11]	No	32	—	Open	Flat	—	Mottled	Fixed flexion	Fixed shortened	Polyhyd.	+	—
Berg et al (2003) [5]	No	36	Hypotelorism	Open	Flat	Dysplastic	Thighs—feet edema	Swollen	Swollen	PPROM	—	IUGR
Bongain et al (2002) [10]	No	30	Ectropion	Open	Flat	Dysplastic	—	Fixed flexion	Bilateral clubfoot	—	—	Subnormal
	+	22	—	Open	Flat	—	—	—	—	Oligohyd.	+	—
Benoit (1999) [9]	No	30	—	Open	Aplasia	Aplasia	—	—	Talipes	Polyhyd.	—	—
Watson and Mabee (1995) [8]	No	21	—	Open	—	—	—	Abnormal position	—	Polyhyd.	—	IUGR
Meizner (1992) [7]	No	31	Ectropion	Open	Aplasia	—	—	Swollen	Swollen	—	—	Normal
Charles et al (1989) [6]	No	23	—	—	—	—	—	Abnormal position	Abnormal position	—	—	—
Mihalko et al (1989) [3]	No	28	Ectropion	—	—	—	Thick floating membrane	—	—	Normal	—	Normal

Ga = gestational age at detection; HI = harlequin ichthyosis; hyd. = hydramnios; IUGR = intrauterine growth restriction; — = not mentioned in the report; + = exist; PPROM = Preterm premature rupture of membranes.

child. The first case of prenatal sonographic diagnosis of HI was reported by Mihalko et al in 1989 [3]. Since then, 12 cases describing the sonographic diagnosis of HI have been published. Sonographic features of our case are discussed herein together with a collation and review of these previous reports. Furthermore, we provide a delineation of the sonographic markers of this rare disorder.

Case report

A 29-year-old woman (gravida 2, para 1) was referred to our unit by another institution at 34⁺⁶ weeks of gestation because of an uncertain fetal malformation. Her first child was born with phenylketonuria. No other relevant issues were found in her obstetric history.

Her first detailed examination had been performed during the 12th week of gestation at Peking Union Medical College Hospital, Beijing, China, which displayed no fetal anatomic malformation. At the same time, the patient underwent chorionic villi sampling for phenylketonuria diagnostic testing, the results of which were normal with a normal karyotype. A routine prenatal two-dimensional sonographic examination during the 2nd trimester performed at the local city hospital was also normal. The next ultrasound scan was performed at 34⁺⁴ weeks of gestation, again at the local city hospital, and the patient was referred to us on the basis of the findings of this scan.

A subsequent ultrasound examination in our center that employed both two- and three-dimensional methods revealed intrauterine growth restriction of the fetus and polyhydramnios. The amniotic fluid appeared cloudy and with increased echogenicity. The most remarkable finding was that the fetus maintained a continuously open mouth with a protruding tongue (Fig. 1). The nose was flat and the eyes were open (Fig. 1). The toes appeared to be short, and the fingers were held in fixed flexion. No fetal movements were seen, including rolling and extension–flexion. The extremities appeared to be fixed in position. A membrane was observed to be floating within the fluid and fixed to the fetal pudendum and thigh skin surface, in addition to a thick membrane that arose from the skin of the wrist (Fig. 2).

Given the tragic prognosis associated with the identified fetal malformations, an early cesarian delivery was suggested and agreed to by the mother. Upon removal of the fetus from the uterus, obvious characteristic features of HI were apparent. The neonate was a female with yellow, thick, and fissured skin. Ectropion and eclabium were noted, and the neonate's nose and ears were hypoplastic. Her limbs were also short and held in a flexed position. The parents declined medical treatment for the neonate in the hospital, choosing to bring her home instead. They were unresponsive to our follow-up attempts after leaving the hospital.

Discussion

Congenital ichthyosis can be divided into three subtypes: lamellar ichthyosis, nonbullous congenital ichthyosiform erythroderma, and HI [4]. HI is the most severe form. As of

2003 (the most recent year for which data are available), 138 cases of HI have been reported; most of these neonates died within their 1st week of life as a result of septicemia [5]. The 12 cases of HI that have been diagnosed by sonography since 1989 are summarized in Table 1 [3,5–15]. Most of these were diagnosed during the 3rd trimester or after birth. The most common and constant sonographic characteristics associated with HI are as follows: a large open mouth (eclabium), a flat nose, abnormal hand and/or foot position, and ectropion. Other associated sonographic features of HI are intrauterine growth restriction, short limbs, intra-amniotic debris, floating membranes, and polyhydramnios. In the present case, almost all these sonographic features were observed, but HI was not definitively diagnosed until after birth.

HI is an autosomal recessive condition, and a 25% recurrence rate enables prenatal diagnosis to be performed for families at risk. Because eclabium and ectropion manifest in the 3rd trimester, a diagnosis of HI based on these findings alone is too late. Early sonographic diagnosis of HI is difficult. Fetal foot length may be an early marker of HI, especially in families with a history of siblings affected by HI [16].

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